

## **REMARKS**

Applicant submits this response to the Office Action dated 26 March 2003. Claims 33, 34, 74-89 and 94-99 are pending in this application. Claims 35-73 and 90-93 are deemed withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as being drawn to a non-elected invention. Applicant has not abandoned the subject matter therein and reserve the right to file a divisional application thereof. Following the above amendments, claims 34, 74-89 and 94-99 have been cancelled and new claims 100-115 have been added. Applicants submit that each of these amendments is supported by the specification as filed and that no new matter has been added. Applicant has not abandoned the cancelled subject matter and reserves the right to file one or more continuation applications directed thereto.

### ***Rejection Under 35 U.S.C. § 112, first paragraph, enablement***

Claims 33, 34, 74-89 and 94-99 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected to make and/or use the present invention. Specifically, the Examiner alleges that the specification, while being enabling for treating cancer *via* the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof obtained from one of the three demonstrated/disclosed *Euphorbia* plant species, does not reasonably provide enablement for treating cancer using any or all compounds, including any or all derivatives of angeloyl-substituted ingenane, obtained from any other *Euphorbia* plant species.

Applicant respectfully traverses this ground of rejection. Applicant respectfully submits that the USPTO has not met its burden establishing that the application is non-enabling. In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1515 (Fed. Cir. 1993). The specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, “it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure.” 439 F.2d at 224, 169 USPQ at 370.

Here, the Examiner has not provided any rationale supporting his allegation that the full scope of the present invention is not enabled. In particular, the Examiner has not cited any reference which refutes the teaching of the present invention. Moreover the Examiner has not provided any evidence which disputes the allegation of the utility of the present invention. The Examiner just renders a conclusion without providing any evidence that supports his belief that any angeloyl substituted ingenane or derivatives thereof derived from any an Euphorbia plant species other than the three identified in the Office Action would not be useful for treating

cancer. Without such evidence, the Examiner has improperly shifted to the burden to the applicant.

Moreover, contrary to the allegations of the Office, the application is enabling. More specifically Applicant submits that the present application is replete with guidance on how one of ordinary skill in the relevant art would treat cancer *via* the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof from any *Euphorbia* plant species. In fact, the Examiner acknowledges that the present specification is enabling for treating cancer *via* the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof obtained from one of the three demonstrated/disclosed *Euphorbia* plant species. Applicant has described in detail, how one of ordinary skill in the relevant art could isolate an angeloyl-substituted ingenane from a *Euphorbia* plant species using routine methodologies, such as HPLC purification, for example, see Examples 1, 2, 3, 4, 6, 7, 8, 9, 10, 11 and 14 for guidance. As further the evidence applicant submits an executed Declaration under 37 C.F.R. §1.132 by the inventor Dr. James Aylward, attached hereto as Exhibit A. The Declaration shows how one of ordinary skill in the art, using the methodologies described in the present specification, were able to isolate various angeloyl-substituted ingenanes from *Euphorbia paralias*. More specifically, the Declaration of Dr. James Aylward describes, how using HPLC purification, a total of sixteen (16) angeloyl-substituted ingenanes were identified from *paralias*. Applicant, therefore, submits that one of ordinary skill in the relevant art without undue experimentation would be able to identify angeloyl-substituted ingenanes from additional *Euphorbia* species.

Having identified an angeloyl-substituted ingenane, one of ordinary skill in the relevant art could then determine, based on the teachings provided in the subject specification, if the isolated angeloyl-substituted ingenane had anti-cancer activity. The present specification is

replete with both *in vitro* and *in vivo* assays on how one would test an angeloyl-substituted ingenane to ascertain its anti-cancer properties. For example, Examples 1, 2, 3, 4, 5, 6, 7, 8 and 9 describe *in vitro* assays, wherein angeloyl-substituted ingenane or compositions comprising angeloyl-substituted ingenane are tested against tumor cell lines for their anti-cancer activity. Further Examples 11 and 12 of the subject specification describe an *in vivo* mouse model which demonstrates the anti-cancer activity of angeloyl-substituted ingenanes or compositions comprising angeloyl-substituted ingenanes. Finally, Example 14 describes a study involving the application of a composition comprising angeloyl-substituted ingenanes to a keratosis on a human subject, wherein the application of the composition resulted in the disappearance of the facial solar keratosis.

Thus, given the level of illustrative guidance in the specification as originally filed, which is supported by the attached Declaration of Dr. James Aylward, Applicant submits that the skilled artisan could readily practice the presently claimed methods of treating cancer via the administration of an effective amount of an angeloyl-substituted ingenane or salt thereof from any *Euphorbia* plant species without undue experimentation.

Moreover, applicant submits that the angeloyl substituted ingenane from the three identified Euphorbia plants are representative of the present invention and evidence the efficacy of the full scope of the present invention. Angeloyl substituted ingenanes are angeloyl substituted ingenanes regardless of the source. Thus, one of ordinary skill in the art reading the application would understand that the angeloyl substituted ingenane from any Euphorbia plant species would be useful for treating cancer. Applicant accordingly submits that the pending claims are fully enabled under 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection is thus respectfully requested.

***Rejection Under 35 U.S.C. § 112, second paragraph***

Claims 33, 34, 74-89 and 94-99 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Specifically, the Examiner alleges that claim 33 is rendered vague and indefinite for reciting the phrase “is capable of inhibiting”. Applicant submits that as claim 33 has been cancelled, and newly added claim 100 corresponding to claim 33 does not recite the phrase “is capable of inhibiting”, this rejection is now moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

The Examiner also alleges that claims 74-77 are rendered vague and indefinite by the phrase “an angeloyl substituted derivative”. Applicant respectfully traverses this ground of rejection. However, for purposes of clarity only, Applicant has elected to cancel claims 74-77 at this time, and added new claims 104 to 106 corresponding thereto which recites in part “wherein the derivative of an angeloyl-substituted ingenane is defined as an acetylated derivative”. For the Examiner’s convenience, Applicant has submitted a second Declaration under 37 C.F.R. §1.132 by Dr. James Aylward attached hereto as Exhibit B which describes the acetylation of Ingenanes. Based therein Applicant submits that one of ordinary skill in the relevant art would understand the metes and bounds of what was meant by the phrase “an angeloyl substituted derivative” in these claims. Reconsideration and withdrawal of the rejection is thus respectfully requested.

The Examiner further alleges that claim 74 is rendered vague and indefinite for the phrase “wherein the compound comprises a composition selected from”, as the recited compounds

thereafter are not compositions per se, but compounds. Applicant submits that as claim 74 has been cancelled, this rejection is now moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

Moreover, the Examiner alleges that claims 95-97 are vague and indefinite for recitation of the phrase “capable of”. Applicant respectfully traverses this ground of rejection. However, Applicant has elected to cancel claims 95-97 at this time, rendering the present rejection moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

In addition, the Examiner alleges that claim 94 is vague and indefinite for recitation of the phrase “wherein the compound further comprises a beta-alanine betaine or a hydroxy-dimethyl proline”. Applicant respectfully traverses this ground of rejection. However, Applicant has elected to cancel claim 94 at this time, rendering the present rejection now moot. Reconsideration and withdrawal of the rejection is thus respectfully requested.

### ***Double Patenting***

Claims 33, 34, 74-83 and 95-98 are rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-12 of US Patent No. 6,432,452. Applicant respectfully traverses the rejection. It is respectfully submitted that the USPTO has not made out a prima facie case of double patenting, as the USPTO concludes that both the subject matter in the rejected claims and claims 1-12 of U.S. Patent No. 6,432,452 are not patentably distinct. But, the USPTO has not made out a prima facie case, as it has not met its burden. Without any evidence, it has concluded both the rejected claims of the present application and claims 1-12 of the ‘452 patent are not patentably distinct. The Office Action has not produced sufficient evidence to support its position. Consequently the rejection

of claims 33, 34, 74-83 and 95-98 under the judicially created doctrine of obviousness type double patenting is obviated; withdrawal thereof is respectfully requested.

***Rejection Under 35 U.S.C. § 102(b)***

Claims 33, 34, 74-77, 84, 93 and 95-98 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hecker *et al.* (U.S. Patent No. 4,716,179). The present invention is, *inter alia*, drawn to a method of treating cancer *via* administering to a subject a compound selected from the group consisting of an angeloyl-substituted ingenane obtained from the sap of an *Euphorbia* species. Hecker *et al.* teach treating a solid tumor *via* administering an antineoplastic composition which comprises an effective amount of a non-irritating or slightly irritating compound obtained from an *Euphorbia* plant including one of various ingenane compounds and derivatives thereof. The Examiner alleges that the various claimed functional effects would be inherent in the referenced compound derivatives.

Applicant respectfully traverses this ground of rejection. Hecker *et al.* do not teach or suggest an angeloyl substituted ingenane. Although some ingenanes are tested, these are not angeloyl substituted, a feature required by the present claims. The Hecker *et al.* reference focuses on the treatment of cancer using an effective amount of a phorbol which has a quite different ring structure than ingenol, let alone an angeloyl ester of ingenol.

As Hecker *et al.* do not teach or suggest an angeloyl substituted ingenanes, as presently claimed, Applicant respectfully submits that the Hecker *et al.* reference does not include each and every limitation of the present claim.

Further, the Hecker *et al.* reference teaches away from the present invention. It discloses, "Many though not all of the presently known irritating diterpene esters of the Daphnane-,

Tigiane- and Ingenane type also have a carcinogenic or qualified cancer-inducing effect”, suggesting that these compounds are in fact associated with causes of cancer and therefore not suitable for use in the treatment of cancer. Applicant submits that such a disclosure teaches away from the use of an ingenane, let alone an angeloyl substituted ingenane, for use in the treatment of cancer. Accordingly, Applicant respectfully requests that the Examiner withdraw this ground of rejection.

Claims 33, 34, 74-77, 84, 85, 89, 93 and 95-98 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Tamas (European Patent No. 0 330 094). Specifically, the Examiner alleges that Tamas teaches treating malignant and non-malignant tumors using an ethanolic extract of *Euphorbia hirta*. According to the Examiner, the present specification discloses that the claimed compound can also be derived from *Euphorbia hirta via*, for example, ethanol extraction. The Examiner concludes that the claimed compound would inherently be present within the reference ethanol extract.

Applicants respectfully traverse this ground of rejection. Applicants submit that nowhere does the Tamas reference teach, suggest or even allude to the use of an angeloyl-substituted ingenane or derivative thereof. The Examiner alleges, however, that the claimed compound would inherently be present within the reference ethanol extract. According to M.P.E.P. § 2112:

“The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic”

M.P.E.P. § 2112, further states that the burden to establish that a certain result or characteristic may occur rests with the Examiner.

Applicants submit that the Examiner has not met its burden of providing evidence which establishes that the compounds of the present invention, namely angeloyl-substituted

ingenanes or derivatives thereof, would be present within the subject ethanol extract. Nor has the Examiner established that the therapeutic effect of the composition described in the Tamas reference was attributable to an angeloyl-substituted ingenanes, rather than an additional component in the ethanol extract used. Accordingly, reconsideration and withdrawal of the rejection is thus respectfully requested.

***Rejection Under 35 U.S.C. § 103(a)***

Claims 33, 34, 74-78 and 94-98 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hecker *et al.* Applicants respectfully traverse this rejection and reiterate the comments hereinabove. As described hereinabove, Hecker *et al.* disclose the use of compounds which are structurally quite different from the angeloyl substituted ingenane or derivatives thereof. It only discloses the use of phorbol derivatives which are quite different from the compounds used in the present invention. Moreover, the Hecker *et al.* reference teaches away from the use of angeloyl substituted ingenanes for treating cancer, since it is alleged that the ingenanes are carcinogenic. Consequently, the rejected claims are patentable thereover. Withdrawal of the rejection is respectfully requested.

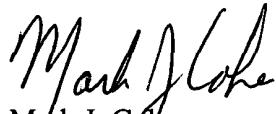
Claims 33, 34, 74-89 and 94-99 stand rejected under 35 U.S.C § 103(a) as allegedly being unpatentable over Tamas and El-Mezabani *et al.* (Planta Med., 1979). Applicant reiterates the comments hereinabove made in relation to the Tamas reference under 35 U.S.C. § 102(b) and incorporate the same by reference. It is respectfully submitted that the Examiner has not made out a prima facie case under 35 U.S.C. §103, as the Official Action has not shown that the therapeutic effect of the compositions described in the Tamas reference was attributable to any angeloyl substituted ingenane rather then to some other component therein.

The secondary reference does not overcome the deficiency of the primary references. In fact, it suffers from the same problem as the primary reference. More specifically, it does not teach, disclose or even suggest that an ingenane let alone an angeloyl substituted ingenane or its derivative is useful for treating cancer. The Examiner has assumed that the secondary reference (as well as the primary reference) inherently disclose the use of angeloyl substituted ingenane, but without any basis, as there is no teaching or suggestion therein for one of ordinary skill in the art to so conclude.

Thus, the combination of two references which do not specify the compounds therein fails to disclose or suggest the use of angeloyl substituted ingenane or derivatives thereof, as claimed, for treating cancer. Therefore, the rejection of the above-identified claims under 35 U.S.C. §103 is overcome; withdrawal thereof is respectfully requested.

Thus, all of the remaining claims in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,



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